1: J Cardiovasc Pharmacol 1996;27 Suppl 3:S26-37

Pharmacology of moxonidine, an I1-imidazoline receptor agonist.

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Moxonidine is a second-generation, centrally acting antihypertensive drug with a distinctive mode of action. Moxonidine activates I1-imidazoline receptors (I1-receptors) in the rostroventrolateral medulla (RVLM), thereby reducing the activity of the sympathetic nervous system. Moxonidine leads to a pronounced and long-lasting blood pressure reduction in different animal models of hypertension, e.g., spontaneously hypertensive rats, renal hypertensive rats, and renal hypertensive dogs. Blood pressure reduction with moxonidine is usually accompanied by a reduction in heart rate which, however, in most studies is of shorter duration and lesser magnitude than the fall in blood pressure. Chronic administration of moxonidine to SHRs with established hypertension causes normalization of myocardial fibrosis, capillarization, and regressive changes in myocytes, in parallel with the reduction of blood pressure. Left ventricular hypertrophy and renal glomerulosclerosis are also significantly reduced. After withdrawal of chronic moxonidine treatment, blood pressure gradually rises to pretreatment values. Direct injection of moxonidine into the vertebral artery of cats elicits a more pronounced fall in blood pressure compared with i.v. injection of an equivalent dose. This observation and others clearly indicate that moxonidine's antihypertensive activity is centrally mediated. The RVLM is the site of action within the CNS that mediates pronounced blood pressure reduction after direct administration of moxonidine into the RVLM of anesthetized SHRs. Selective I1-receptor antagonists introduced into this area abolish the action of systemic moxonidine. Receptor binding studies have shown high and selective affinity of moxonidine for I1-receptors vs. alpha(2)-adrenergic receptors. In vivo studies using a variety of selective I1 or alpha(2)-adrenergic agonists and antagonists have confirmed the primary role of I1-receptors in blood pressure regulation by moxonidine. In addition to lowering blood pressure, moxonidine possesses further properties that appear likely to be relevant in its therapeutic application in the hypertensive syndrome. Moxonidine increases urine flow rate and sodium excretion after central and direct intrarenal administration. It is active against ventricular arrhythmias in a variety of experimental settings. It lacks the respiratory depressant effect attributed to central alpha 2 activation. It exerts beneficial effects

on glucose metabolism and blood lipids in genetically hypertensive obese rats. It exhibits anti-ulcer activity. And, finally, moxonidine lowers intraocular pressure, suggesting a possible benefit in glaucoma. Therefore, moxonidine, by its novel mode of action, represents a new therapeutic principle in the treatment of hypertension. Because of its unique profile, moxonidine may prove to be effective in slowing progression of the disease by providing protective effects beyond merely blood pressure reduction. Further studies are needed to verify this potential.

Publication Types:
- Review
- Review, Academic

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Acute hemodynamic and neurohumoral effects of moxonidine in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy.

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Elevated plasma norepinephrine (PNE) has been shown to be an important predictor of morbidity and mortality in patients with congestive heart failure (CHF). Moxonidine selectively stimulates imidazoline receptors located in the medulla, which centrally inhibit sympathetic outflow. PNE is suppressed and peripheral vasodilation reduces systemic blood pressure. This study evaluated the acute neurohumoral and hemodynamic effects of a single dose of oral moxonidine in 32 patients (22 men, mean +/- SD age 66 +/- 10 years) with CHF. All patients were in New York Heart Association functional class III and stabilized on chronic therapy with diuretics, digitalis, and angiotensin-converting enzyme inhibitors. The mean PNE concentration was 509 +/- 304 pg/ml at baseline. Patients underwent invasive hemodynamic monitoring after double-blind randomization to either placebo (n = 12), moxonidine 0.4 mg (n = 9), or moxonidine 0.6 mg (n = 11). Moxonidine produced a dose-dependent, vasodilator response compared with placebo. Analysis of the time-averaged change from baseline over 6 hours demonstrated that moxonidine 0.6 mg caused significant reductions in mean systemic arterial pressure ($p < 0.0001$), mean pulmonary arterial pressure ($p < 0.005$), systemic vascular resistance ($p < 0.05$), pulmonary vascular resistance ($p < 0.01$), and heart rate ($p < 0.05$). Stroke volume was unchanged. PNE was reduced substantially (-180 pg/ml at 4 hours, $p < 0.005$) and the reduction was highly correlated with the baseline level ($r = -0.968$). Moxonidine was well tolerated in this single-dose study and resulted in a modest, dose-dependent, vasodilator response, with substantial reductions in systemic and pulmonary arterial blood pressure. Trials designed to evaluate the clinical efficacy of chronic moxonidine therapy in CHF added to conventional therapy would be appropriate.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

1: Eur J Pharmacol 2000 May 26;397(1):113-20 Related Articles, NEW Books, LinkOut

FULL-TEXT ARTICLE

Chronic administration of moxonidine suppresses sympathetic activation in a rat heart failure model.

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Excessive sympathetic activity contributes to cardiovascular abnormalities, which negatively affect the prognosis of heart failure. The present study evaluated the effects of moxonidine, an imidazoline I(1) receptor agonist, on sympathetic activation and myocardial remodelling in a rat heart failure model. Rats were subjected to coronary artery ligation, and treated with moxonidine, 3 or 6 mg/kg/day, from 1 to 21 days after myocardial infarction. After 21 days, heart rate and blood pressure were measured in conscious, chronically instrumented rats. Plasma catecholamine levels were determined by high-performance liquid chromatography. Effects on post-myocardial infarction remodelling were evaluated from the ventricular weight body weight ratio and interstitial collagen deposition, measured morphometrically in the interventricular septum remote from the infarcted area. Moxonidine dose-dependently decreased myocardial infarction induced tachycardia but did not affect myocardial infarction reduced blood pressure. Plasma noradrenaline levels, which were elevated after myocardial infarction, decreased below sham-values with 6 mg/kg/day moxonidine. Ventricular weight-body weight ratio as well as interstitial collagen were significantly elevated in myocardial infarcted rats, and restored to sham values with 6 mg/kg/day moxonidine. These data suggest that moxonidine suppresses myocardial infarction induced sympathetic activation in a dose-dependent way as indicated by reduced heart rate and plasma noradrenaline levels. Furthermore, post-myocardial infarction remodelling may be attenuated at a higher dose-range of moxonidine as shown by normalisation of ventricular weight body weight ratio and interstitial collagen.

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Thrombolytic therapy for acute myocardial infarction-effects, problems and strategies.

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The effects and problems of coronary thrombolysis (CT) were investigated in 652 patients with initial acute myocardial infraction (AMI). Nosocomial mortality obtained by matching factors which determined prognosis was significantly lower in patients treated by CT (8.3%) than in those who did not undergo CT (18.1%). Regardless of whether the treatment was intracoronary arterial (ICT) or intravenous (IVCT), the primary cause of the decreased mortality was reperfusion of the coronary artery responsible for infarction (mortality 6.1% in the reperfused group vs 21.5% in the ineffective group). CT therapy improved left ventricular ejection fraction (LVEF), the nosocomial mortality rate, and regional wall motion at the site of infarction in cases that were reperfused less than 3 h, 3-6 h, and even 6 or more hours after the therapy. The long-term prognosis was significantly better in the reperfused group than in the ineffective group for 5 years and 7 months after therapy. However, CT was accompanied by both (1) poor prognosis in the ineffective group; and (2) unfavorable effects on the prognosis and on the daily life of patients with severe stenosis even after treatment. Accordingly, supplemental ICT and rescue PTCA (strategy (A)) were performed to treat the first problem, and deferred PTCA (strategy (B)) was conducted to treat the second problem in 80 patients with initial AMI. As a result, strategy (A) increased the coronary reperfusion rate to 94.3%, and strategies (A) and (B) together decreased the nosocomial mortality rate of 8.5% to 3.8%, and reduced the risk of death by 55.3%.

PMID: 7699735 [PubMed - indexed for MEDLINE]

[Imidazoline receptors and use of drug blocking receptors I1]

[Article in Polish]

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Imidazoline-preferring receptors are important in the pathophysiology of hypertension. The selective I1-receptor agonists are moxonidine, cimetidine and rilmenidine. Some clinical studies indicate the usefulness of moxonidine therapy in hypertension, arrhythmias and acute myocardial infarction.

Publication Types:

- Review
- Review, Tutorial

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Effect of moxonidine on arrhythmias induced by coronary artery occlusion and reperfusion.

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The aim of the present study was to investigate the influence of moxonidine, a representative of I1-imidazoline-receptor agonist, on arrhythmias induced by myocardial ischemia or reperfusion. Acute myocardial infarction was produced by tightening a previously placed loose silk loop around the coronary artery in conscious rats. Moxonidine (0.01, 0.03, or 0.10 mg/kg i.v., 10 min before coronary ligation) significantly decreased the incidence of ventricular tachycardia during the first 15 min of infarction (70 versus 100% in controls), and the number of animals that survived without developing any arrhythmia was increased (15, 20, and 25%, respectively, versus 0%). Reperfusion-induced arrhythmias were produced by releasing a snare after 6 min of myocardial ischemia in anesthetized, artificially ventilated rats. Reperfusion rapidly induced severe dysrhythmias in all of the control animals. Moxonidine pretreatment (0.03 and 0.10 mg/kg) decreased the incidence of ventricular fibrillation (25 and 30% versus 64%) and increased the number of animals that survived without developing any arrhythmia (20 and 25% versus 0%). We conclude that moxonidine offers significant protection against the development of arrhythmias induced by acute regional myocardial ischemia in conscious rats. Moxonidine pretreatment also provides a beneficial effect during reperfusion-induced arrhythmias that appear after a brief period of myocardial ischemia.

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